AD_____

Award Number: DAMD17-00-1-0422

TITLE: Adequacy of Chemotherapy Dose Intensity Among African-American Women with HER-2/neu-Positive Breast Cancer

PRINCIPAL INVESTIGATOR: Jennifer J. Griggs, M.D.

CONTRACTING ORGANIZATION: University of Rochester
Rochester, New York 14627

REPORT DATE: September 2002

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2002	Annual (1 Sep 01 - 31 Aug 02)

4. TITLE AND SUBTITLE
Adequacy of Chemotherapy Dose Intensity Among African-American Women with HER-2/neu-Positive Breast Cancer

5. FUNDING NUMBERS
DAMD17-00-1-0422

6. AUTHOR(S):
Jennifer J. Griggs, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Rochester
Rochester, New York 14627

E-Mail: jennifer_griggs@urmc.rochester.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The purpose of this study is to investigate the possibility that systematic differences in the quality of adjuvant chemotherapy given to African-American and Caucasian women account for the poorer outcome in African-American women. We will determine the impact of these differences on outcome, particularly in patients whose tumors overexpress HER-2/*neu* (in whom chemotherapy dose is particularly important). The analysis described in this report includes 489 subjects (109 African-American and 380 non-Hispanic Caucasian) who received adjuvant chemotherapy between 1985 - 1995 in two geographical locations. Chemotherapy dose proportion (actual/predicted doses) and dose intensity were determined for each drug and for the regimen. Using multivariate regression models, we have demonstrated that African-American ethnicity is an independent predictor of lower dose proportion and dose intensity (correcting for sociodemographic, tumor characteristics, and treatment course). The mean dose proportion among African-American women is .80 compared with .85 among Caucasian women ($p = .02$). In multivariate analyses, race/ethnicity was significantly associated with lower dose proportion ($p = .002$) and dose intensity ($p = .001$). During Year 3, we will be analyzing the data to determine the impact of adjuvant chemotherapy dose proportion and intensity on outcome in subjects with HER-2/*neu* positive breast cancer.

14. SUBJECT TERMS	15. NUMBER OF PAGES
breast cancer, racial disparity, quality of care	13
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Introduction

Although the risk of breast cancer in African-American women is lower than in Caucasian women, African-American women have higher breast cancer fatality and case-fatality rates(1). The disparity in breast cancer outcome is not accounted for solely by differences in stage at diagnosis or in the biologic behavior of the disease(2). Differences in the quality of chemotherapy received by African-American women may provide an additional explanation for the poorer outcome among African-American women. Retrospective analyses suggest the beneficial impact of adjuvant chemotherapy on disease-free and overall survival in women with breast cancer is diminished when full doses of therapy are not received (3;4). The current recommendation is that patients undergoing adjuvant chemotherapy for breast cancer receive at least 80 to 85 percent of the planned doses (5). This multicenter study focuses on the clinical impact of suboptimal dose/dose intensity in women with HER-2/*neu*-positive tumors, a subgroup in whom optimal chemotherapy may be particularly critical. We are investigating the potential of relative chemotherapy dose (the ratio of actual to predicted doses) and dose intensity (which incorporates time to completion of adjuvant chemotherapy) as measures of quality of care. This study involves review of treatment records of subjects who have received chemotherapy for breast cancer and identification of the HER-2/*neu* oncogene on archival tumor specimens. The primary measures of chemotherapy quality (relative dose and dose intensity) will be related to the subjects' clinical outcome. The ultimate goal of the project is to design interventions targeting those factors that lead to lower dose intense chemotherapy in an effort to eliminate disparities in the quality of care of women with breast cancer.

Research Progress (Body)

Three sites are participating in this study as outlined below. Eligible subjects are women who were treated with adjuvant chemotherapy for stage I, II, or III breast cancer between 1985 and 1995.We are enrolling a total of 500 subjects at the three sites.

As of the date of this report, we are on schedule according to the approved Statement of Work submitted with the original grant application. Relocation of the Principal Investigator at Singing River Health System, Dr. Raymond Wynn and extensive changes in the management of clinical research have continued to delay progress at this site as described below.
We have completed the following work:

Task 1. Identify eligible subjects by HER-2/neu staining on primary tumor samples and begin preparation for data collection, Months 1-12

a. Identify 500 eligible subjects at the three participating sites
b. Process and send samples for staining at central laboratory
c. Stain and interpret HER-2/*neu* staining in African-American subjects and Caucasian controls
d. Design database in preparation for data abstraction

Identification of Subjects
(Task 1a)

University of Rochester (Rochester, New York)
Using the Monroe County Tumor Registry and direct abstraction from chemotherapy (medical oncology) treatment records, we have identified 175 eligible subjects treated for primary breast cancer at Strong Memorial Hospital between 1985 and 1995. Twenty-four are African-American, and 151 are non-Hispanic Caucasian. Demographic and treatment records have been retrieved and preliminary data collected and recorded on each eligible subject. Tumor blocks for all primary breast tumors have been located for all subjects (see Tasks 1b and 1c, below).

Henry Ford Health System (Detroit, Michigan)
Of 100 African-American and 100 Caucasian patients treated for primary breast cancer between 1990 and 1995 at the Henry Ford Health System, 158 are eligible and have complete information. (The dates of inclusion for eligible subjects are restricted by competition for tumor blocks within the Henry Ford Health System.) Review of the treatment records has been completed with quality checks for consistency and accuracy of the data. Tumor blocks for 100 subjects have been retrieved as of the date of this report (see Tasks 1b and 1c, below).

Singing River Health System (Pascagoula, Mississippi)
Due to relocation of the Principal Investigator at this site (R. Wynn) to Singing River and major changes in the procedures required for approval of research studies, there had been delays in regulatory approval at this site. Approval by the Institutional Review Board at the Singing River Health System was delayed and only obtained in December 2001. Identification of subjects is complete, and data abstraction on 25 subjects is finished. We anticipate that subjects will be eligible at this site.

Retrieval and Processing of Primary Breast Cancer Tumor Blocks
(Tasks 1b and 1c)

University of Rochester (Rochester, New York)
Tumor blocks of the primary breast tumors have been retrieved and processed for 95% of the deceased subjects (deceased n = 35). For subjects who are surviving but have recurrent disease (n = 24), most have had HER-2/*neu* staining performed on their primary tumors. This staining was performed (using the same methodology as for this study) solely for the purposes of appropriately treating their recurrent disease according to clinical practice and *not* for the purposes of this or any other research project. For the subjects who are surviving with no evidence of recurrent disease (n = 117), informed consent is being sought to perform HER-2/*neu* testing on the primary tumor blocks. As of this date, these subjects have been identified with a plan in place for approaching them through their treating oncologists (as outlined in the approved protocol). Because visits to the treating oncologist are infrequent in subjects who were diagnosed in 1985 through 1995 and are free of disease (occurring only once a year if at all), we have had to revise our estimate of the time required to obtain consent from these subjects. Eight subjects have provided consent for HER-2 staining of their primary tumors, and staining is complete.

Interpretation of the stained slides for overexpression of HER-2/*neu* will be completed by the middle of Year 3. We are on target to finish this portion of the study within Year 3, save for the staining in subjects who are free of disease who need to be approached for informed consent (as described above).

Henry Ford Health System (Detroit, Michigan)
Of 100 African-American and 100 Caucasian patients treated for primary breast cancer between 1990 and 1995 at the Henry Ford Health System, 158 are eligible and have complete information. (As described above, the dates of inclusion for eligible subjects are restricted by competition for tumor blocks within the Henry Ford Health System.) Tumor blocks for 100 subjects have been retrieved as of the date of this report (see Tasks 1b and 1c, below), and all blocks have been processed and stained. Interpretation of HER-2/*neu* overexpression on these samples was completed this year. Six of the blocks need to be re-cut and processed.

Singing River Health System (Pascagoula, Mississippi)
As described above, the relocation of the Principal Investigator at this site (R. Wynn) to Singing River and major changes in the procedures required for approval of research studies have led to delays in regulatory approval at this site. Approval by the Institutional Review Board at the Singing River Health System was obtained December 14, 2001. Identification of subjects is complete, and data abstraction on 25 out of 132 eligible subjects is complete.

Database Design
(Task 1d)

We have designed and refined a comprehensive database for data entry for subjects in this study using Access 97® (Microsoft Corporation). A copy of the worksheet version of this database was attached as Appendix A for the annual report from Year 1. Data entry is being performed by the Study Coordinator at the University of Rochester.

Task 2. Abstraction of data from records of women whose tumors stain positive for overexpression of HER-2/*neu*, Months 13-24

a. Train data managers in data abstraction
b. Complete data abstraction from records of eligible subjects (approximately 40 subjects at each site = 160 total)
c. Complete data entry and confirm consistency of data abstraction methods

Train Data Managers in Data Abstraction
(Task 2a)

The data manager at Henry Ford Health System has been trained in the abstraction of data from the medical records with quality controls checks performed during the first 12 months of the

study. The Principal Investigator and the Study Coordinator at the University of Rochester have been responsible for quality checks of the data. The Study Coordinator at Singing River Health System has been trained and has started data collection. Quality checks will be performed continuously.

Data Abstraction from Records of Eligible Subjects
(Task 2b)

With funding from the Doris Duke Charitable Foundation and additional support, we have been able to complete data abstraction on all subjects who meet criteria—including subjects with both HER-2 positive and HER-2 negative tumors. (Of note, this revision was advised by the grant reviewers for this project as well, but we needed additional support.) The findings reported below are with all subjects.

University of Rochester (Rochester, New York)
We have completed medical record review for the 175 eligible subjects at this site. Chemotherapy data are available on 100% of the subjects. Some subjects were excluded for some analyses because of incomplete data.

Henry Ford Health System (Detroit, Michigan)
Complete data abstraction has been performed on 158 subjects.

Singing River Health System (Pascagoula, Mississippi)
As described above, approval of this protocol by the Institutional Review Board at the Singing River Health System was delayed only on December 14, 2001. Data abstraction is underway, and we have complete data on 25 subjects. The Study Coordinator will be completing data abstraction in the first half of Year 3.

Data Entry and Confirm Consistency of the Data Abstraction
(Task 2c)

Data entry is ongoing as described above with continuous monitoring of the quality of data by the Principal Investigator and the Study Coordinator at the University of Rochester.

Task 3. Analysis of data, Months 25-36

a. Design multivariate regression models
b. Conduct analyses
c. Interpret data with investigators in Consortium
d. Begin designing interventions based upon results

We are currently in Month 14 of the project. Data analysis is the major focus of Year 3 (months 25-36) of this project. Preliminary analyses of the data obtained at the University of Rochester

(funded by this grant and additional foundation funding sources and presented in abstract form in Appendices B) demonstrate that chemotherapy differences do exist between the two racial/ethnic groups. African-American women received, on average, less of the planned chemotherapy doses, with a lower mean dose intensity among this group of subjects. The mean dose *proportion* among minority women was .80 compared to .85 among non-minority women ($p = .03$). The mean dose *intensity*, which incorporates the time required for completion of therapy, among the minority women was .76 compared to .80 among non-minorities ($p = .01$). Multivariate regression models were used to assess to determine the contribution of race/ethnicity, age, socioeconomic status, clinical factors, treatment regimen, and treatment site to the dose proportion and dose intensity of the chemotherapy regimen. In these multivariate models, African-American ethnicity was significantly associated with lower dose proportion ($p = .002$) and dose intensity ($p = .001$). Co-existing medical conditions and tumor stage were not associated with the dose proportion or dose intensity.

We have also found that physician prescribing patterns varied among different patient ethnic/racial groups. Dose reductions before the start of therapy (up-front dose reductions) were more common among minority women, even after correction for obesity (previously an indication for such dose reductions). A logistic regression model was developed to determine the relationship between ethnicity, obesity, socioeconomic status and to the likelihood of upfront dose reduction, controlling for age, year of treatment, socioeconomic status, baseline white blood cell counts, tumor stage, co-existing medical conditions, treatment regimen, and treatment site. Sixteen percent of women received an upfront dose reduction. In bivariate analyses, African-American women were only slightly more likely to have an upfront dose reduction than Caucasian women (15% versus 18%, $p=0.49$). In multivariate analyses, however, African-American ethnicity was associated an significantly increased likelihood of having an upfront dose reduction (OR 3.7, $p = 0.02$). Living in a census block with a high per capita income was associated with a reduced likelihood of having an upfront dose reduction (OR=0.49, $p=0.04$), while co-existing medical conditions, age at diagnosis, tumor stage, and regimen were not significant predictors. In the early 1990's, recommended medical practice shifted towards using actual rather than ideal body weight in obese women. In our model, being treated before 1993 was associated with a higher likelihood of upfront dose reduction among obese women (OR=3.48, $p<0.001$), suggesting that providers changed prescribing patterns in response to the recommendations in the literature.

Our results suggest that ethnicity predicts suboptimal chemotherapy for early stage breast cancer. Our findings also suggest the presence of prescriber bias in the decision to reduce chemotherapy doses at the start of treatment. Women who are obese, African-American, and living below the median income are most likely to receive reduced chemotherapy doses. This phenomenon may contribute to the higher case-fatality rate among African-American women and economically disadvantaged women with breast cancer.

The current project is examining the impact of such dose reductions on outcome and the generalizability of our findings to two other distinct geographic locales. If our findings are consistent among the different treatment sites included in this study and if the dose/dose intensity of adjuvant chemotherapy has an impact on outcome, interventions to eliminate the disparities in

the quality of chemotherapy have the potential to improve the quality of care for minority women with breast cancer.

Key Research Accomplishments

1. We have developed a network of breast cancer treatment sites.
2. We have demonstrated the feasibility of abstraction of specific chemotherapy treatment details at disparate treatment facilities.
3. We have developed a data collection system, comprehensive database, and statistical program to calculate dose and dose intensity of a variety of chemotherapy regimens for early-stage breast cancer.
4. We have demonstrated that disparities exist among different ethnic/racial groups in the administration of chemotherapy for early-stage breast cancer.
5. We have also shown that obesity impacts chemotherapy prescribing patterns.

Reportable Outcomes

1. "Ethnicity and Age Predict Suboptimal Adjuvant Chemotherapy for Breast Cancer," Abstract and Podium Presentation, Annual Meeting of the Academy of Health Services Research, June 2001.
2. "Do Physician Prescribing Patterns Differ by Ethnicity in the Treatment of Localized Breast Cancer?" Abstract, Annual Meeting of the Academy of Health Services Research, June 2001.
3. "Racial Disparities in the Quality of Adjuvant Chemotherapy among Women with Early Breast Cancer" (manuscript in preparation to be submitted soon to the Journal of the National Cancer Institute).
4. "Racial Disparity in Breast Cancer Chemotherapy," Presentation at the Henry Ford Health System Cancer Center Grand Rounds, November 30, 2001.
5. Database, Access 97® (Microsoft Corporation) for entry of subject-specific data across all study sites.
6. "Racial Variation in Breast Cancer Adjuvant Therapy," Cancer Center Grand Rounds, Medical College of Virginia, Richmond, Virginia, February 2002.
7. "Quality of Breast Cancer Adjuvant Chemotherapy in African-American and Caucasian Women," accepted for Poster Presentation, San Antonio Breast Cancer Symposium, San Antonio, Texas, December 2002 (upcoming).
8. Grant application, National Cancer Institute (R21), "Racial Disparities in Breast Cancer Adjuvant Therapy," favorable reviews, not within funding range. Resubmission planned for February or June 2003.

Conclusions

We have demonstrated that the collection of detailed chemotherapy treatment information is feasible across study sites.

More important are the findings of our preliminary analyses that support our hypothesis that disparity exists in the quality of adjuvant chemotherapy for localized breast cancer among ethnic/racial and socioeconomic groups. Our results suggest that ethnicity predicts suboptimal chemotherapy for early stage breast cancer. Our findings also suggest the presence of provider bias in the decision to reduce chemotherapy doses at the start of treatment. Women who are obese, African-American, and living below the median income are most likely to receive reduced chemotherapy doses. This phenomenon may contribute to the higher case-fatality rate among African-American women (and economically disadvantaged women) with breast cancer.

Thus far, our measures are process measures of quality of care. If such dose reductions have an impact on outcome and the findings are generalizable to two other distinct geographic locales, we have developed a novel measure of quality of care. Interventions to eliminate the disparities in the quality of chemotherapy have the potential to improve the quality of care for minority women and economically disadvantaged women with breast cancer.

Management of localized breast cancer is complicated and requires coordination of care across multiple specialties. The project thus far has raised the possibility that the process of care differs between racial/ethnic and socioeconomic groups. We are applying for additional funding to expand this research program. Plans for ongoing work, in addition to that outlined in Tasks 2 and 3 including examining other patterns of care, such as (1) delays from diagnosis to surgery, (2) delays from surgery to the initiation of chemotherapy, (3) delays in the initiation or completion of adjuvant radiotherapy, (4) differences in side effects among different racial groups, and (6) differences in the use of supportive therapies such as granulocyte-colony stimulating factor.

Once such disparities have been identified, the impact of the patterns of care on outcome will be determined. The ultimate goal is to design interventions to eliminate, or at least mitigate, such disparities. Developing the infrastructure for such interventions is a major goal of this research program.

Reference List

(1) Ries, L. A. G., Eisner, M. P., Kosary, C. L., Hankey, B. F., Miller, B. A., Clegg, L., and Edwards, B. K. SEER Cancer Statistics Review, 1973-1998. 2001. Bethesda, MD, National Cancer Institute.

(2) Eley JW, Hill HA, Chen VW, Austin DF, Wesley MN, Muss HB et al. Racial differences in survival from breast cancer. Results of the National Cancer Institute Black/White Cancer Survival Study. JAMA. 1994;272:947-54.

(3) Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. New England Journal of Medicine. 1981;304:10-15.

(4) Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. New England Journal of Medicine. 1995;332:901-6.

(5) Goldhirsch A, Gelber RD. Understanding adjuvant chemotherapy for breast cancer. New England Journal of Medicine. 1994;330:1308-9.

Appendix A

List of Personnel:

University of Rochester

PI	Jennifer J. Griggs, MD, MPH
Pathologist	Linda M. Schiffauer, MD
Sr. Project Coord.	Susanne Heininger, RN

Henry Ford Health System

Site Investigator	Azadeh Stark, PhD
Site Project Coord.	Gena Kucera, MPH
Histotechnologist	Bridget Elington

Singing River Health System

Site Investigator	Raymond B. Wynn, MD
Data Manager	Carolyn Freeman

Appendix B

Quality of Breast Cancer Adjuvant Chemotherapy in African-American and Caucasian Women. JJ Griggs, MES Sorbero, Azadeh Stark. University of Rochester, Departments of Medicine, Hematology/Oncology and Community and Preventive Medicine, and Henry Ford Health System, Detroit, Michigan.

Breast cancer mortality rates are consistently higher in African-American women than in Caucasian women. This disparity is outcome is not fully accounted for by differences in stage or biology of the disease. **Objective**: The purpose of this multicenter study was to determine whether or not there are systematic differences in the quality of adjuvant chemotherapy (defined as dose proportion and dose intensity) received by African-American and Caucasian women. **Methods**: We performed detailed audit of medical oncology chemotherapy treatment records in 435 subjects (91 African-American and 344 non-Hispanic Caucasian) who received adjuvant chemotherapy with a cyclophosphamide-containing regimen between 1985 and 1995 in one of ten treatment sites. Data collected included demographic and clinical characteristics and information regarding height, weight, chemotherapy doses, dates, dose reductions, white blood cell counts, side effects, and complications. Chemotherapy dose proportion (actual/predicted doses) and dose proportion (which incorporates the time required for completion of chemotherapy) were determined for each drug and for the regimen. Multivariate regression models were designed to determine the impact of self-defined ethnicity, age, socioeconomic variables, coexisting medical conditions, regimen, site, and year of treatment on dose proportion and dose intensity. **Results**: African-American subjects received significantly lower dose proportion and dose intensity than Caucasian women. The mean dose proportion among African-American women was .79 compared with .85 among Caucasian women ($p = .02$). The mean dose intensity among African-American women was .73 compared with .81 among Caucasian women ($p = .004$). In multivariate analyses, race/ethnicity was significantly associated with lower dose proportion ($p = .03$) and dose intensity ($p = .005$). **Conclusion**: The disparity in breast cancer outcome between African-American women and Caucasian women may be due in part to the receipt of suboptimal adjuvant chemotherapy among African-American women.

Accepted for poster presentation at the San Antonio Breast Cancer Symposium, San Antonio, Texas, December 2002 (upcoming).